Applications of Glyconanoparticles

Glyconanoparticles are expected to have an unlimited number of therapeutic and diagnostic applications – particularly in areas of currently unmet medical need.

By Dr David McL Hill at Midatech

Dr David McL Hill graduated from Surrey University with a degree in Medical Biochemistry, and from Dundee University with degrees in Medicine and Surgery. Following a hospital career in paediatrics, clinical chemistry and metabolic medicine, he started work in the pharmaceutical industry as a Medical Advisor with Sterling Research. His career has focused on R&D with companies such as Medeva, but more recently he has taken on roles that are more management- and commercially-oriented whilst also having an R&D element to them. Before taking on his role at Midatech, he was CEO of SR Pharma.

Nanoparticles offer the possibility to create a whole new variety of products with novel characteristics, functions and applications. The technology can be applied to solve drug delivery problems, to attach multiple ligands for drug tissue targeting, for the production of multivalent vaccines and for the delivery of siRNA or DNA.

Midatech is developing a patent-protected glyconanoparticle (GNP) technology platform developed by the CSIC (Consejo Superior de Investigaciones Cientificas) in Seville, Andalusia, Spain. Each glyconanoparticle has three potentially variable components – the metal core, the linker and the ligand (see Figure 1). These nanoparticles are the smallest produced to date (~800 picometers); they are water-soluble and can be derivatised at the self-assembly stage to contain up to 90 different ligands including lipids, carbohydrates, peptides, DNA, RNA or essentially any chemical entity. The nanoparticle cores can contain either a passive metal such as gold, or any combination of active metal to give the core functional properties.

Midatech’s technology offers the following:

- Very small nanoparticles
- A particle surface that resembles a cell membrane
- The ability to add a variety of ligands separately or together to one particle to create a multi-functional nano platform by established methods, covalently linking drugs or functional bio-molecules such as DNA or antigens
- The highest possible surface density of bioactivity
- Non-denaturing environment enables binding of bio-molecules without impairing their functionality
- The highest possible orientation of polyvalent ligands and accessibility of defined functional domains
- Tissue specific targeting
- Flexibility in particle design – charge, solubility, magnetic properties
- Thermal and chemical stability

THERAPEUTIC APPLICATIONS

Progress in novel DNA and RNA technology applications has been hampered by a number of problems – in particular, poor stability of antisense oligonucleotides, nuclease activity in vitro and in vivo and low intracellular penetration. While short interfering RNAs (siRNAs) may have superseded antisense, issues remain with regard to stability, cell penetration and non-specific aptameric affects (leading to non-specific binding of siRNAs). The use of targeted or ‘stealth’ carriers – such as nanoparticles – has been considered as an optimal solution to overcome these problems.

The problems of gene delivery, vector immunogenicity and gene stability have to be overcome for their use in the treatment or prevention of genetic disorders based on the delivery of repaired or the replacement of incorrect genes. In nanotechnology-based gene therapy, the viral vectors used at present would be replaced by potentially less immunogenic nano-size gene carriers. Vectors based on nanoparticles can be developed to transport plasmid DNA.
In addition to utilising GNP magnetic properties for imaging, advantage can also be taken of this property for therapeutic applications. The presence of gold in the composite Au/Fe GNP makes the nano crystals susceptible to heating through hysteresis by applying an alternating current magnetic field. This will increase the local temperature of the bound molecule on the cell – resulting in localised heat dissipation and the potential killing of a tumour cell, bacteria or virus.

Glyconanoparticles, acting as ‘stealth’ vectors, can be used as delivery vehicles for short siRNAs for down-regulating a target gene. As down-regulation may be transient in effect, the nanoparticles could be linked to a radionuclide or other agent for treating or killing the cells in which the nanoparticles down-regulate the target genes.

Anti-adhesive therapeutics (inhibition of selectin or glycosaminoglycan mediated interactions) and cell-signalling therapeutics (heparan sulphate bioactive sequences) are another key area of application. GNPs can act as therapeutics in inflammatory, adhesion and aggregation conditions, auto-immune diseases, infections and cancers involving carbohydrate-mediated interactions. Specific examples include leucocyte-endothelial cell adhesion, post-surgery adhesions, blood platelet aggregation, carbohydrate-antibody interactions, carbohydrate-protein bacterial and viral infections, immunological recognition of tumour cells, tumour cell-endothelial cell (for example, metastasis), and foreign tissue and cell recognition (auto-immune diseases and cancers).

**TARGETED DRUG DELIVERY**

The most talked about area for the application of nanotechnology is drug delivery. The current estimate of the global market for drug delivery products is US$33 billion per annum, with growth of around 15% per year. A relatively small number of products drive this huge market.

Eight per cent of many ordinary drugs taken orally are destroyed by the stomach or removed by the liver. The ideal drug delivery system gets around this metabolism by allowing the delivery of drugs to a specific target when needed, and in controlled doses related to the patient’s requirements. This means the reduction of unwanted side effects, improvement in patient compliance and lower dose levels – the latter offering potential for the use of drugs that have previously been considered to be too toxic. An additional advantage of targeted and controlled drug delivery is that, as treatments are more effective, there are pharmacoeconomic benefits.

The therapeutic potential of many currently available molecules is severely hampered by instability issues and the difficulties involved in passing through certain biological barriers. Nanoparticles can address these problems. Some drugs which – for biopharmaceutical and technological reasons – have not attained their full therapeutic potential may be more beneficial if administered in nanoparticulate form.

The sheer variety of chemical constructs that can create GNPs makes it extremely difficult to generalise on their application in drug delivery. The beauty of GNPs lies in the fact that they can be designed and synthesised for specific applications, as truly functional drug delivery

![Figure 1: Structure of a glyconanoparticle showing the three potentially variable components – the metal core, the linker and the ligand](image-url)
systems (see Figure 2). GNP\textsuperscript{s} offer the control that modern drug delivery and targeting demands:

- Control of the chemical nature of the carrier – defining delivery characteristics
- Control of drug presentation – protection of potentially degradable moieties
- Control of the surface, internal structure and character, which are vital in drug targeting
- Control of molecular weight
- Control of dimensions

Exquisite \textit{in vivo} targeting specificity can be achieved with magnetic glyconanoparticles. Ultimately, the synthesis of multifunctional nanosystems associated with these homing particles could form the basis of devices which sense the presence of disease, deliver a drug to the disease site and then release the drug at that site.

**VACCINE AND ANTI-ADHESIVE TECHNOLOGY**

Vaccines represent an opportunity for glyconanoparticles to deliver early 'proof of principle' for the technology; it could, for instance, make a significant impact in post-operative metastasis of tumours. There is a general acceptance that the process of tumour metastasis and subsequent localisation of the metastasis is mediated by cell/cell interactions between the tumour cells and the endothelium. Such interactions are initially mediated by carbohydrate/carbohydrate and carbohydrate/protein (selectin) interactions. The prevention of tumour cells from migrating from the intravascular to the extra-vascular space could make a significant impact on the efficiency of tumour metastasis, especially in post-operative scenarios.

Initial experiments in mice infected with melanoma cell-lines, incubated with GNP\textsuperscript{s} that displayed the relevant carbohydrate structures, have suggested facilitation of the first selective molecular recognition step of the adhesion/transmigration process. The experiments yielded promising results, in that a clear inhibitory effect to the adhesion of the metastases \textit{in vitro} could be detected.

Early work with other GNP constructs has shown the ability to induce a variety of immune responses ‘by design’ – including antibodies against defined tumour antigen targets. Research is currently being carried out on the ability to enhance these responses by adding very specific immune-response modifiers.

Glyconanoparticles offer considerable advantages in the area of vaccines at two levels: first, targeting of cell-cell interactions; and second, targeted immune responses in communicable and non-communicable diseases.

In particular, they offer:

- Delivery of key tumour-related or infectious agent-related antigens
- The ability to target defined cells
- The facility to add specific immune response-inducers to the particle, thereby directing the required immune response
- Particle characteristics that mimic the cell wall, thereby creating a target for the primary immune response

**IMAGING AND DIAGNOSTICS**

\textit{In Vivo} Imaging

Over the last 25 years, non invasive imaging techniques have made a considerable impact on medical diagnosis. As always, there is room for improvement, and for developing techniques such as functional MRI, there is a need to enhance contrast agents and spatial resolution.

One of the most pressing needs in clinical oncology, for example, is for imaging agents that can identify tumours that are far smaller than can be detected with today's technology. To achieve this improvement in sensitivity, there needs to be a better targeting of imaging agents and the generation of a bigger imaging signal. Nanotechnology could have an early ‘paradigm-changing’ impact on how clinicians detect diseases at their earliest stages, as nanoscale devices prove to be capable of accomplishing improved targeting and image enhancement.
Ultimately, Midatech aims to create water-soluble, stable and biologically active Quantum dots for use in screening and therapeutic techniques.

CONCLUSION

Midatech is the only provider of custom-designed nanoparticle products and services to the research, pharmaceutical and biopharmaceutical community. Its vision is to become a leader in the application of nanotechnology in medicine by directed use of the glyconanoparticle technology platform to a wide range of products for the health care industry. The company is building a state-of-the-art manufacturing facility capable of producing cGMP glyconanoparticles, and also a custom-designed research and development facility at the Technology Park in Bilbao.

Glyconanoparticles are a versatile tool for many therapeutic and diagnostic applications. Because of their versatile nature, they offer the opportunity to achieve the integration of all of their potential applications into a single product. The National Cancer Institute (NCI) in the US has set this as their target (see http://nano.cancer.gov/). This is summarised in Figure 3. From a commercial point-of-view, the key is to target the technology to areas where there are genuine unmet needs. These areas include cancer, the treatment and diagnosis of solid tumours, vaccines for cancer and infectious diseases, the delivery of siRNA and drug delivery.

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